BEST AVAILABLE COPY

mailroom date 7-28-00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Jordan J.N. Tang and Arun K. Ghosh

Serial No.: 09/506,988 Art Unit:

Filed: February 18, 2000 Examiner: Not Yet Assigned

For: *PROTEASE INHIBITORS THAT OVERCOME DRUG RESISTANCE*

Assistant Commissioner for Patents
Washington, D.C. 20231

INFORMATION DISCLOSURE STATEMENT

Sir:

Pursuant to 37 C.F.R. §1.56 and 37 C.F.R. §1.97, Applicants submit an Information Disclosure Statement, including six (6) pages of Form PTO-1449 and a copy of each document cited therein.

This Information Disclosure Statement is being filed under 37 C.F.R. § 1.97(b) prior to a first Office Action on the merits. It is believed that no fee is required with this submission. However, should a fee be required, the Commissioner is hereby authorized to charge any required fees to Deposit Account No. 01-2507.

Publications

BALDWIN, et al., "Structural basis of drug resistance for the V82A mutant of HIV-1 proteinase," *Nat. Struct. Biol.* 2(3):244-9 (1995).

BOGER, "Renin Inhibitors. Design of Angiotensinogen Transition-state Analogs Containing Statine:Conformationally restricted inhibitors and a model for the bound conformation of renin substrate," in Aspartic Proteinases and Their Inhibitors. (Kostka, V., ed.). pp. 401-420. Walter de Gruyter:N.Y., 1985.

CARPENTER, et al., "Antiretroviral therapy for HIV infection in 1998: Updated recommendations of the International AIDS Society-USA Panel," *JAMA* 280(1):78-86 (1998).

CARROLL, et al. "Identification of potent inhibitors of *Plasmodium falciparum* plasmepsin II from an encoded statine combinatorial library," *Bioorg. Med. Chem. Lett.* 8(17):2315-20 (1998).

CARROLL, et al., "Evaluation of a structure-based statine cyclic diamino amide encoded combinatorial library against plasmepsin II and cathepsin D," *Bioorg. Med. Chem. Lett.* 8(22):3203-6 (1998).

CHEN, et al., "Three-dimensional structure of a mutant HIV-1 protease displaying cross-resistance to all protease inhibitors in clinical trials," *J. Biol. Chem.* 270(37):21433-6 (1995).

COFFIN, "HIV population dynamics in vivo: implications for genetic variation, pathogenesis, and therapy," *Science* 267(5197):483-9 (1995).

CONDRA, et al., "Genetic correlates of in vivo viral resistance to indinavir, a human immunodeficiency virus type 1 protease inhibitor," *J. Virol.* 70(12):8270-6 (1996).

CONDRA, et al., "*In vivo* emergence of HIV-1 variants resistant to multiple protease inhibitors," *Nature* 374(6522):569-71 (1995).

CRAIG, et al., "Antiviral properties of Ro 31-8959, an inhibitor of human immunodeficiency virus (HIV) proteinase," *Antiviral Res.* 16(4):295-305 (1991).

DEBOUCK & METCALF, "Human Immunodeficiency Virus Protease: A target for AIDS therapy," *Drug Devel. Res.* 21:1-17 (1990).

DEBOUCK, et al., "Human immunodeficiency virus protease expressed in *Escherichia coli* exhibits autoprocessing and specific maturation of the gag precursor," *Proc. Natl. Acad. Sci. USA* 84:8903-8907 (1987).

DORSEY, et al., "L-735,524: the design of a potent and orally bioavailable HIV protease inhibitor," *J. Med. Chem.* 37(21):3443-51 (1994).

DUNN, et al., "Subsite preferences of retroviral proteinases," *Methods Enzymol.* 241:254-178 (1994).

ERMOLIEFF, et al., "Kinetic properties of saquinavir-resistant mutants of human immunodeficiency virus type 1 protease and their implications in drug resistance *in Vivo*," *Biochemistry* 36(40):12364-70 (1997).

GHOSH, et al., "An efficient synthesis of hydroxyethylene dipeptide isosteres: The core unit of potent HIV-1 protease inhibitors," *J. Org. Chem.* 56:6500-3 (1991)

GHOSH, et al., "3-tetrahydrofuran and pyran urethanes as high-affinity P_2-ligands for HIV-1 protease inhibitors," *J. Med. Chem.* 36:292-94 (1993).

GRAVES, "Human immunodeficiency virus proteinase: now, then, what's next?" *Adv Exp Med Biol.* 306:395-405 (1991).

GULNIK, et al., "Kinetic characterization and cross-resistance patterns of HIV-1 protease mutants selected under drug pressure," *Biochemistry* 34(29):9282-7 (1995).

HO, et al., "Rapid turnover of plasma virions and CD4 lymphocytes in HIV-1 infection," *Nature* 373(6510):123-6 (1995).

HONG, et al., "Crystal structures of complexes of a peptidic inhibitor with wild-type and two mutant HIV-1 proteases," *Biochemistry* 35:123-126 (1996).

HONG, et al., "Active-site mobility in human immunodeficiency virus, type 1, protease as demonstrated by crystal structure of A28S mutant," *Protein Sci.* 7(2):300-5 (1998).

HOOVER, et al., "Discovery of inhibitors of human renin with high oral bioavailability," *Adv Exp Med Biol.* 362:167-80 (1995).

IDO, et al., "Kinetic studies of human immunodeficiency virus type 1 protease and its active-site hydrogen bond mutant A28S," *J. Biol. Chem.* 266(36):24359-66 (1991).

JACOBSEN, et al., "Characterization of human immunodeficiency virus type 1 mutants with decreased sensitivity to proteinase inhibitor Ro 31-8959," *Virology* 206(1):527-34 (1995).

JACOBSEN, et al., "In vivo resistance to a human immunodeficiency virus type 1 proteinase inhibitor: mutations, kinetics, and frequencies," *J. Infect. Dis.* 173(6):1379-87 (1996).

KEMPF, et al., "ABT-538 is a potent inhibitor of human immunodeficiency virus protease and has high oral bioavailability in humans," *Proc. Natl. Acad. Sci. USA.* 92(7):2484-8 (1995).

KOHL, et al., "Active human immunodeficiency virus protease is required for viral infectivity," *Proc. Natl. Acad. Sci. USA* 85(13):4686-90 (1988).

DUNN, et al., "Subsite Preferences of Retroviral Proteinases" *Methods in Enzymology* 241:254-278 (1994).

LAPATTO, et al., "X-ray analysis of HIV-1 proteinase at 2.7 A resolution confirms structural homology among retroviral enzymes," *Nature* 342(6247):299-302 (1989).

LIN, et al., "Effect of point mutations on the kinetics and the inhibition of human immunodeficiency type 1 protease: Relationship to drug resistance," *Biochemistry* 34:1143-1152 (1995).

MAJER, et al., "Structure-based subsite specificity mapping of human cathepsin D using statine-based inhibitors," *Protein Sci.* 6(7):1458-66 (1997).

MARCINISZYN, et al., "Mode of inhibition of acid proteases by pepstatin," *J. Biol. Chem.* 251(22):7088-94 (1976).

MELLORS, "Closing in on human immunodeficiency virus-1," *Nat. Med.* 2(3):274-5 (1996).

MOLLA, et al., "Ordered accumulation of mutations in HIV protease confers resistance to ritonavir," *Nat. Med.* 2(7):760-6 (1996).

MULICHAK & WATENPAUGH, "The crystallographic structure of the protease from human immunodeficiency virus type 2 with two synthetic peptidic transition state analog inhibitors," *J. Biol. Chem.* 268(18):13103-9 (1993).

NAVIA, et al., "Three-dimensional structure of aspartyl protease from human immunodeficiency virus HIV-1," *Nature* 337(6208):615-20 (1989).

PATICK, et al., "Antiviral and resistance studies of AG1343, an orally bioavailable inhibitor of human immunodeficiency virus protease," *Antimicrob. Agents Chemother.* 40(2):292-7 (1996).

PENG, et al., "Role of human immunodeficiency virus type 1-specific protease in core protein maturation and viral infectivity," *J. Virol.* 63(6):2550-6 (1989).

POORMAN, et al., "A cumulative specificity model for proteases from human immunodeficiency virus types 1 and 2, inferred from statistical analysis of an extended substrate data base," *J. Biol. Chem.* 266(22):14554-61 (1991).

RIDKY & LEIS, "Development of drug resistance to HIV-1 protease inhibitors," *J. Biol. Chem.* 270(50):29621-3 (1995).

RIDKY, et al., "Human immunodeficiency virus, type 1 protease substrate specificity is limited by interactions between substrate amino acids bound in adjacent enzyme subsites," *J. Biol. Chem.* 271:4709-4717 (1996).

ROCHEFORT, "Biological and clinical significance of cathepsin D in breast cancer," *Semin. Cancer Biol.* 1(2):153-60 (1990).

ROSE, et al., "Human immunodeficiency virus type 1 viral background plays a major role in development of resistance to protease inhibitors," *Proc. Natl. Acad. Sci. USA* 93(4):1648-53 (1996).

SCHNEIDER & KENT, "Enzymatic activity of a synthetic 99 residue protein corresponding to the putative HIV-1 protease," *Cell* 54(3):363-8 (1988).

SIMAN, et al., "Processing of the beta-amyloid precursor. Multiple proteases generate and degrade potentially amyloidogenic fragments," *J. Biol. Chem.* 268(22):16602-9 (1993).

SZELKE, "Chemistry of Renin Inhibitors," in, Aspartic Proteinases and Their Inhibitors, (Kostka, ed.), pp. 421-441, (Walter de Gruyter:N.Y., 1985).

TANG & HARTSUCK, "A kinetic model for comparing proteolytic processing activity and inhibitor resistance potential of mutant HIV-1 proteases," *FEBS Lett.* 367(2):112-6 (1995).

TOH, et al., "Is the AIDS virus recombinant?" *Nature* 316(6023):21-2 (1985).

TOMASSELLI, et al., "The complexities of AIDS: An assessment of the HIV protease as a therapeutic target," *Chimicaoggi-Chemistry Today* 9:6-27 (1991).

TONG, et al., "Crystal structure of human immunodeficiency virus (HIV) type 2 protease in complex with a reduced amide inhibitor and comparison with HIV-1 protease structures," *Proc. Natl. Acad. Sci. USA* 90(18):8387-91 (1993).

TOWLER, et al., "Functional characterization of the protease of human endogenous retrovirus, K10: can it complement HIV-1 protease?" *Biochemistry* 37(49):17137-44 (1998).

VACCA, "Design of Tight-Binding Human Immunodeficiency Virus Type 1 Protease Inhibitors," *Methods in Enzymology* 241:311-334 (1994).

WEI, et al., "Viral dynamics in human immunodeficiency virus type 1 infection," *Nature* 373(6510):117-22 (1995).

WEISS, et al., RNA Tumor Viruses, Cold Spring Harbor:NY, 1984.

WLODAWER & ERICKSON, "Structure-based inhibitors of HIV-1 protease," *Annu. Rev. Biochem.* 62:543-85 (1993).

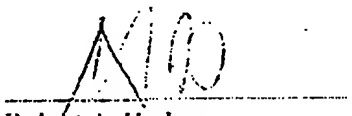
WLODAWER, et al., "Conserved folding in retroviral proteases: crystal structure of a synthetic HIV-1 protease," *Science* 245(4918):616-21 (1989).

U.S.S.N.: 09/506,988
Filed: February 18, 2000
INFORMATION DISCLOSURE STATEMENT

Remarks

This statement should not be interpreted as a representation that an exhaustive search has been conducted or that no better art exists. Moreover, Applicants invite the Examiner to make an independent evaluation of the cited art to determine its relevance to the subject matter of the present application. Applicants are of the opinion that their claims patentably distinguish over the art referred to herein, either alone or in combination.

Respectfully submitted,



Robert A. Hodges
Reg. No. 41,074

Dated: July 25, 2000

ARNALL GOLDEN & GREGORY, LLP
2800 One Atlantic Center
1201 West Peachtree Street
Atlanta, Georgia 30309-3450
(404) 873-8796
(404) 873-8797 (fax)